REMARKS

Claims 1-37 were previously canceled without prejudice to the Applicants' rights to pursue the subject matters in a future application. Claims 38-76 were previously added and are currently pending in this application. By this Amendment, Applicants added new claims 77-121. Support for claims 77-121 may be found *inter alia* on page 38, lines 35-36 and page 39, lines 1-3 of the Specification as filed. Therefore, there is no issue of new matter and Applicants respectfully request the entry of this Amendment. Upon entry, claims 38-121 are pending and under examination.

I. The Obviousness Criteria

To reject claims in an application under U.S.C. § 103, an unrebutted prima facie case of obviousness must be established by an examiner. In Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 U.S.P.Q (BNA) 459, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966), the Supreme Court articulated the four (4) factual inquiries for determining obviousness under 35 U.S.C. § 103(a), namely:

(1) the scope and content of the prior art;
(2) the differences between the prior art and the claimed invention;
(3) the level of ordinary skill in the field of the invention; and
(4) an objective indicia such as (i) commercial success, (ii) long felt need, (iii) unexpected results created by the claimed invention, (iv) copying by others, (v) licensing to others, (vi)skepticism of skilled artisans or (vii) failure of others. *In re Rouffet*, 149, F.3d 1350, 1355 (Fed. Cir. 1998).

Most if not all inventions arise from a combination of old elements. See *In re Rouffet* at 1357. Thus, most elements of a claimed invention may often be found in the prior art. See id. 1357. When the claimed invention is made by combining known components to achieve a new system, the prior art must provide a ***suggestion or motivation*** to make such a combination *[emphasis added]. C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1351 (Fed. Cir. 1998)(quoting Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc., 21 F.3d 1068, 1072 (Fed. Cir. 1993)). It is insufficient that prior art shows similar components, unless it also contains some teaching, suggestion, or incentive for arriving at the claimed structure. *Id.* at 1351 (quoting Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 934 (Fed. Cir. 1990)). It is impressible to reconstruct the claimed invention from selected pieces of prior art absent some suggestion, teaching, or motivation in the prior art to do so. *C.R. Bard, Inc. v. M3 Systems, Inc.* at 1352. The examiner may not use the claimed invention as a blueprint to elements in the prior art to defeat the patentability of the claimed invention. *In re Rouffet* at 1357.

To prevent the use of hindsight based on the invention to defeat patentability of the invention, the examiner must show reasons that a person of ordinary skill in the art, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior references for combination in the manner claimed. *Id.* at 1357.

Motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of a person of ordinary skill in the art, or, in some cases the nature of the problem to be solved. *In re Werner Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). Teaching, motivation or suggestion may also

be implicit from the prior art as a whole. *Id.* at 1370. The test for an implicit showing is what the combine teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art. *Id.* at 1370.

II. Claim Rejections - 35 U.S.C. § 103

A. Claims 38-53 are Not Obvious under 35 U.S.C. § 103(a) over Anuta and Lehtinen

The Examiner to whom this Application is assigned (the "Examiner") rejected claims 38-53 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,341,691 ("Anuta") and U.S. Patent No. 5,733,564 ("Lehtinen et al").

Applicants' independent claim 38 reads as follows:

> 38. A composition useful as local drug delivery system comprising:
>
> (a) a polymeric bone-cement component in the form of particles, and
>
> (b) an anti-resorptive agent in the form of particles,
>
> wherein the anti-resorptive agent's particle-size distribution is about the same or less than the polymeric bone-cement component's particle-size distribution.

Dependent claims 39-46 are drawn to bisphosphonates, pamidronate, etidronate, alendronate, zoledronate, gallium fluoride, cholesterol-lowering agents, estrogen-bisphosphonate conjugate as anti-resorptive agents. In an embodiment, 65 to about 70 percent of the particles in the claimed composition have an average diameter of about 25 microns. See claim 50. In another embodiment, 30 to about 35 percent of the particles in the claimed composition are about 13 to 17 microns in diameter. See claim 51.

1. Scope and Content of the Prior Art

(a) Lehtinen et al Patent

Lehtinen et al possibly disclose or teach:

> A method for treating un-cemented endo-osteal materials by immersing the endo-osteal material in an aqueous solution containing bisphosphonate of formula (I); and
>
> An un-cemented endo-osteal materials treated with a solution containing bisphosphonate of formula (I).

See Lehtinen et al, U.S. Patent No. 5,733,564 for formula (I) ("clodronate").

Examiner contends that Lehtinen et al discribed that "bisphosphonate's main effect is their ability to inhibit resorption." Examiner concedes that Lehtinen et al do not teach zoledronate, pamidronate, etidronate or alendronate.

The Examiner further concedes that Lehtinen et al do not teach particle size distribution as recited in dependent claim 50 and 51.

(b) Anuta Patent

Anuta teaches:

> A bone cement comprising a liquid monomer and a polymer powder or beads component.

The Examiner contends that Anuta teaches:

> "The poly methyl methacrylate powder in Zimmers standard bone cement is comprised of a mixture of 65% to 70% polymer beads with a maximum average size of 25 microns **and** 30 to 35% of the beads have been milled **and** a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns."

The Examiner cites column 5, lines 43-47 of Anuta patent as support.

The Examiner concedes that Anuta "does not teach the addition of bisphosphonates."

2. Differences Between the Prior Art and the Claimed Invention

(a) Lehtinen et al Patent

Lehtinen et al do not teach or suggest: zoledronate, pamidronate, etidronate or alendronate; particle-size distribution as recited in dependent claim 50 and 51; composition for local drug delivery; particle-size distribution of the anti-resorptive component relative to the bone-cement component; and composition w/ a cement-component and an anti-resorptive component in the form of particles.

Lehtinen et al describe a pre-treatment strategy to saturate "endo-osteal" materials with bisphosphonates to stimulate bone growth into the materials while this Application claims a drug delivery system for the release of antiresorption agents to the entire inner surface area of bone to inhibit the osteoclast activity associated with aseptic loosening. The Lehtinen et al deal with a scheme to encourage bone formation into the prosthesis while the claimed invention relates to the inhibition of bone resorption.

The bisphosphonate soaked "endo-osteal" materials described within Lehtinen et al do not claim to be a drug delivery system for anti-resorptive drugs to inhibit aseptic loosening. Rather the Lehtinen et al relate to pretreating "endo-osteal" materials prior to implant to enhance bone ingrowth in cementless prosthesis. The claimed invention seeks to arrest the process of aseptic loosening attributed to osteoclasts and associated with cemented prosthesis. The claimed invention

provides an effective means to locally deliver drug to regional bone because the alternative means of administration, i.e. intravenous and oral, have been ineffective.

Moreover, Lehtinen et al do not apply to the repair of bony deficits in flat bones, i.e. spine following tumor removal to inhibit tumor recurrence and enhance the support capacity of the remaining bone.

In addition, this Application claims chemical formulations for novel orthopaedic products/devices. The antiresorption agent within the bone-cement is a solid that is slowly leached from the cement directly to the adjacent bone and is intended to stop the process of bone resorption. Bone ingrowth into the cement is not intended, required or produced. The antiresorption agent - cement provides positional alignment and structural stability in addition to its role as a drug delivery system. Alternatively, bone ingrowth is a requirement for cementless prosthesis; Lehtinen et al disclose a soaking process to address this requirement.

Furthermore, the Examiner concedes that Lehtinen et al do not teach zoledronate, pamidronate, etidronate or alendronate; however, the Examiner contends that "it would have been obvious to one of ordinary skill in the art at the time it was made to substitute zoledronate, pamidronate, etidronate or alendronate, all bisphosphonates, for the clodronate of the prior art."

(b) Anuta Patent

Anuta does not teach or suggest: anti-resorptive agents in the form of particles; particle-size distribution of the anti-resorptive component is about the same or less than the polymeric bone-cement component; and a composition for local drug delivery.

The Examiner contends:

> "It would have been made obvious to one of ordinary skill in the art at the time it was made to employ the recited particle sizes motivated by the recitation of Anuta that Zimmer's standard bone cement employs a mixture of 65 to 70% polymer beads with a maximum average size of 25 microns **and** 30 to 35% of the beads have been milled **and** a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns."

However, Applicants respectfully maintain that broad claim 38 and dependent claims 50 and 51 do not contain the limitations as stated by the Examiner, namely:

(1) Applicants' claim 38 does not recite specific particle size;

(2) While Applicants' claim 50 recite a composition where 65 to about 70 percent of the particles have an average diameter of about 25 microns, the particle size of the remaining 35 to about 30 percent of the particles are not necessarily limited to a size range of 13 to 17 microns as stated by the Examiner; and

(3) While Applicants' claim 51 recite a composition where 30 to about 35 percent of the particles are about 13 to about 17 microns in diameter, the particle size of the remaining 65 to about 70 percent of the particles are not necessarily limited to a size range of about 25 microns as stated by the Examiner

3. Level of Ordinary Skill in the Field of the Invention

The decision of obviousness is made from the viewpoint a person of ordinary skill in the field of invention. *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 956

(Fed. Cir. 1997). The purpose for articulating the level of ordinary skill is to assure "an appropriate perspective of the decision maker, and to focus on the conditions as they existed when the invention was made." *Id.* at 956. Good ideas may appear "obvious" after they have been disclosed, despite having been previously unrecognized. *Id.* at 956.

The Examiner alleged that "it would have been obvious to employ a bisphosphonate in the bone cement..."; however, the level of ordinary skill with no knowledge of Applicants' claimed invention that is needed to combine the teachings of Lehtinen et al and Anuta to make the claimed composition was not addressed.

4. Objective Indicia

Objective indicia of nonobviousness or "secondary consideration" provide evidence of how the patent device is viewed by the interested public. *Id.* at 957. Evidences of secondary consideration may be highly probative of the issue of nonobviousness. *Id.* at 957. It may often establish that an invention appearing to have been obvious in light of prior art was not. *Id.* at 957.

Here, Applicants have unexpectedly discovered that if the particle-size distribution of the anti-resorptive agent is about the same as the bone cement, a uniform mixture will result which prevents clumping thereby promoting the even distribution of the anti-resorptive agent in the composition. If the anti-resorptive agent is not evenly distributed, the agent may seep out of the cured cement at different rates and/or in different peripheral areas (a problem that has been encountered in using non-uniform mixtures of bone-cement and anti-resorptive particles.)

B. Nonobviousness Determination

The Examiner contends:

> "It would have been obvious to employ a bisphosphonate in the bone cement movtivated by the teaching of Lehtinen et al who teach that bisphosphonate's main effect is their ability to inhibit bone resorption. Such a modification would have been motivated by the reasoned expectation of producing a bone cement which is effective in comprehensively inhibiting bone resorption."

In response, Applicants respectfully traverses the Examiner's above ground of rejection.

1. No prior art showed or suggested the combination of bone-cement with anti-resorptive agent for effective local delivery of therapeutic compounds

A showing of a suggestion, teaching, or motivation to combine the prior art references is an essential component of an obviousness holding. There must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab,* 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000).

On the matter of motivation to combine the Lehtinen et al and Anuta references, the Examiner contends that "it would have been obvious to employ a bisphosphonate in the bone cement movtivated by the teaching of Lehtinen et al... a modification would have been motivated by the reasoned expectation of producing a bone-cement which is effective in comprehensively inhibiting bone resorption." However, the Examiner does not particularly identify any suggestion, teaching, or motivation to combine Lehtinen et al and Anuta, nor does the Examiner

make specific reasons concerning the identification of the relevant art, the level of ordinary skill in the art, or the nature of the problem to be solved. Examiner's conclusory statement fails to demonstrate how Lehtinen et al and Anuta references teach or suggest their combination -- to make a composition with a bone-cement component and an anti-resorptive component for delivering drugs locally.

2. No prior art showed or suggested the combination of bone-cement with anti-resorptive agent where the anti-resorptive agent's particle-size distribution is about the same or less than the polymeric bone-cement component's particle-size distribution

As previously stated, Applicants have also unexpectedly discovered that if the particle-size distribution of the anti-resorptive agent is about the same as the bone cement, a uniform mixture will result which prevents clumping thereby promoting the even distribution of the anti-resorptive agent in the composition. See for example page 17, lines 20-23. If the anti-resorptive agent is not evenly distributed, the agent may seep out of the cured cement at different rates and/or in different peripheral areas (a problem that has been encountered in using non-uniform mixtures of bone-cement and anti-resorptive particles.) Anuta and Lehtinen et al alone or in combination do not teach, disclose or suggest mixing anti-bone resorptive particles with polymeric bone-cement particles which have substantially the same particle-size distributions. Preparation of a formulation must consider: 1) the drug delivery potential of the cement, 2) the physiological response of adjacent bone to the final drug level achieved by the formulation (See for example page 32, lines 8-10) and 3) the effect of the formulation on the biomechanical properties. See for example page 37, lines 7-23. Finally, the claimed formulation considers the anti-tumor effects of the formulation (See for example, page 32, lines 28-31), which is

neither claimed nor suggested by Anuta or Lehtinen et al alone or in combination.

3. Examiner has also failed to explain what specific understanding or technical principal would have suggested the combination

(a) Combination of Lehtinen et al and Anuta would change the principle operation of Applicants' claimed invention

The combination of a solution of clodronate, a bisphosphonate, with polymeric bone-cement particles would change the principal operation of the Applicants' claimed invention and render it unsatisfactory and inoperable for its intended purpose. In addition, any aqueous solution will inhibit polymerization. See for example page 18, lines 35-36 and page 19, lines 1-12. Furthermore, cementing a prosthesis treated with clodronate to the bone of a subject does not read on Applicants' claimed invention because Applicants' claimed invention can, in addition to inhibiting bone resorption and securing prostheses to the bone of a patient, deliver large quantities of drugs directly to the adjacent bone to inhibit osteoclast mediate osteolysis. See for example page 37, lines 1-6. In contrast, Lehtinen et al is for un-cemented prostheses.

(b) Combination of Lehtinen et al and Anuta do not disclose, teach or suggest interactions between bone-cement and drugs to produce Applicants' claimed invention

In addition, the combined teachings of Anuta and Lehtinen et al do not disclose, teach or suggest the mechanical effects of anti-resorptive drug, which would require a detailed understanding of chemistry interactions between polymer and the drug. When an anti-resorptive agent is used with bone cement, there is a physical entrapment (e.g. impregnation) of the anti-resorptive agent in the bone cement. See for example page 34, lines 29-32. The success of a formulation depends upon the chemistry of the bone-cement polymer. For example,

it has been determined that Biomet PMMA releases more than twice the amount of pamidronate as Simplex PMMA. As a result the drug content can be reduced to achieve equivalent dose with the added advantage that strength will be improved. Furthermore, neither Lehtinen et al nor Anuta teach (1) the consideration of the temperature stability of the anti-resorptive agents; (2) hydration state of the anti-resorptive agent and its impact on cement polymerization or setting; or (3) the effect of the chemical reaction of the bone-cement on the anti-resorptive agent. See for example page 18, line 32-36 and page 19, line 1-6.

Accordingly, for the reasons stated above, Applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

C. Claims 54-76 are Not Obvious under 35 U.S.C. § 103(a) over Mao and Gayer

The Examiner rejected claims 54-76 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,238,687 B1 ("Mao") and U.S. Patent No. 6,214,049 B1 ("Gayer").

Applicants' representative claim 54 recites:

> A composition comprising:
>
> (a) a bone-cement selected from the group consisting of (1) an organic cement, (2) an inorganic cement, and (3) a composite cement; and
>
> (b) an anti-resorptive amount of an anti-resorptive agent wherein the anti-resorptive amount of an anti-resorptive agent
>
> wherein the anti-resorptive agent is present in an amount that does not compromise the cement's chemical or mechanical properties.

1. Scope and Content of the Prior Art

(a) Mao et al Patent

The Examiner contends that Mao et al teach:

> "Polymeric materials that can be used to produce surgical devices such as molded appliances. The polymers can be used in a composition containing an active substance and can be used to produce a bone cement for repairing injury to bone. The other active agents that can be added to the bone cement are anti-neoplastics, estrogenic substances, cholesterol-lowering agents…"

(b) Gayer et al Patent

The Examiner contends that Gayer et al teach:

> "Moldable polymer matrix systems for bone replacement. The polymer may contain hydroapatite and osteoconductive factors such as bisphosphonate."

2. Differences Between the Prior Art and the Claimed Invention

(a) Mao et al Reference

Mao et al possibly disclose the use of specific ***biodegradable*** polymers which **degrade** in vivo that can be used as a bone-cement with certain bioactive materials.

In contrast, the bone cement of the Applicants' claimed invention is intended to be used to bond to the prosthetic implants to the bone of a patient for substantially the life of the patient.

(b) Gayer et al Reference

Gayer et al possibly disclose an ***uncemented*** prosthetic implant/device containing fibrillar wires. The fibrillar wires

are coated with osteoconductive factors to stimulate bone growth through the fibrillar wires.

In contrast, the claimed invention seeks to arrest the process of aseptic loosening attributed to osteoclasts and associated with cemented prosthesis. The anti-resorption agent within the bone cement is a **solid** that is **slowly leached** from the cement directly to the adjacent bone and is intended to stop the process of bone resorption. Bone ingrowth into the cement, is not intended, required or produced. The anti-resorption agent cement provides positional alignment and structural stability in addition to its role as a drug delivery system. Alternatively, bone ingrowth is a requirement for cementless prosthesis; the Gayer et al disclose an adding fibrillar wires to uncemented prosthetic implants to address this requirement.

3. Level of Ordinary Skill in the Field of the Invention

As previously stated, the purpose for articulating the level of ordinary skill is to assure "an appropriate perspective of the decision maker, and to focus on the conditions as they existed when the invention was made." *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.* at 956. However, the level of ordinary skill with no knowledge of the invention that is needed to combine the teachings of Lehtinen et al and Anuta to make Applicants' claimed invention was not addressed.

D. Nonobviousness Determination

The Examiner contends that Mao et al teach polymeric materials that can be used to produce surgical devices such as molded appliances. However, it is Applicants' understanding that Mao et al disclose the use of specific **biodegradable** polymers that can be used as a bone-cement formulated with certain bioactive materials useful only for ***repairing*** injuries to bone or

connective tissue. In contrast, the bone-cement matrix of Applicants' invention can be used to bond prostheses to the bone of a patient for an extended period time, and does not degrade over time.

Gayer et al relate to **un-cemented** prosthetic implant device containing fibrillar wires coated with osteoconductive factors for stimulating new bone formation or regeneration. In contrast, Applicants' claimed invention is intended to be used to *secure prosthetic implants to the bone* [*emphasis*] of a patient for substantially the life of the patient.

1. **No prior art showed or suggested the combination of bone-cement with anti-resorptive agent to secure prosthetic implants to the bone of a patient where the bone-cement would be bonded to the bone for substantially the life of the patient**

The combination of Mao et al and Gayer et al in an attempt to derive the Applicants' invention would change the principal operation of the Applicants' claimed invention and render it unsatisfactory and inoperable for its intended purpose.

Applicants' claimed invention relates to a non-degradable, bone-cement matrix containing anti-resorptive agents for inhibiting bone resorption and for drug delivery, and the anti-resorptive agent is physically entrapped in the bone-cement matrix. Mao et al and Gayer et al, alone or in combination, do not disclose, teach or suggest Applicants' claimed invention, which is using bone-cement containing anti-resorptive agents to bond prosthetic implants to the bone of a patient for substantially the life of the patient.

The combination of Mao et al and Gayer et al would result in prosthesis with fibrillar wires coated with biodegradable polymer composition, which if used as bone-cement for bonding prosthesis to the bone of a patient would ***result in joint***

failure as the bone-cement polymer matrix would degrade over time.

Furthermore, Gayer et al refer only to un-cemented prostheses. No where does Mao et al not even disclose, teach or suggest a bone-cement for bonding **prostheses to the bone of a patient** *[emphasis]*.

Accordingly, for the reasons stated above, Applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

Conclusion

Applicants believe that the above arguments address all issues raised in the June 24, 2004 Office Action and respectfully request the reconsideration and withdrawal of all ground of rejections pending in this application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee other than the SEVEN HUNDRED AND TWENTY-FOUR DOLLARS ($724.00) for the extra claims fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

I hereby certify that this paper is being deposited this date with the U.S. Postal Service with sufficient postage for first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Albert Wai Kit Chan 9/24/04

Albert Wai-Kit Chan Date
Reg. No. 36,479

Respectfully submitted,

Albert Wai Kit Chan

Albert Wai-Kit Chan
Registration No. 36,479
Attorney for Applicants
Law Offices of
Albert Wai-Kit Chan, LLC
World Plaza, Suite 604
141-07 20th Avenue
Whitestone, New York 11357
Tel: (718) 357-8836
Fax: (718) 357-8615
E-mail: kitchanlaw@aol.com